UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,708	06/19/2006	Thalaththani Ralalage Vedananda	PC/4-33275A	1613

75074 7590 10/09/2008

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
400 TECHNOLOGY SQUARE
CAMBRIDGE, MA 02139

EXAMINER	
RODRIGUEZ-GARCIA, VALERIE	

ART UNIT	PAPER NUMBER
4161	

MAIL DATE	DELIVERY MODE
10/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,708	VEDANANDA, THALATHTHANI RALALAGE	
	Examiner	Art Unit	
	VALERIE RODRIGUEZ-GARCIA	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *9,10 and 16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 11-15* is/are rejected.

7)☐ Claim(s) ___ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

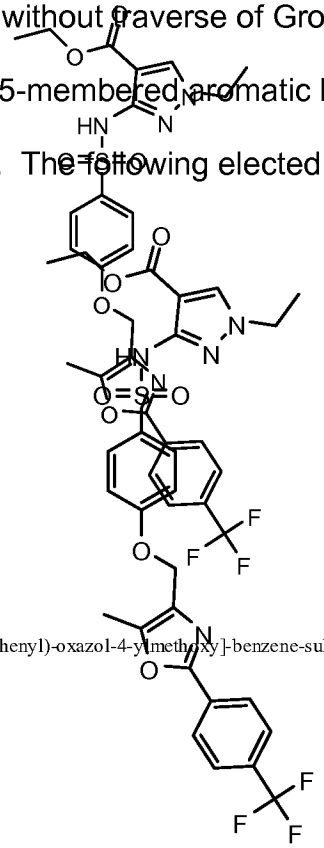
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-21 are currently pending. Claims 22-31 were canceled by applicant.

1. Applicant's election without traverse of Group I, claims 1-8 and 11-15 where Z= oxygen, Q= bond and W= 5-membered aromatic heterocycle, in the reply filed on 08/11/08 is acknowledged. The following elected species is also acknowledged:



1-ethyl-3-[4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzene-sulfonylamino]-1H-pyrazole-4-carboxylic acid ethyl ester

1-ethyl-3-[4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzene-sulfonylamino]-1H-pyrazole-4-carboxylic acid ethyl ester

Claims 9-10 and 16-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 08/11/08.

Claims 1-8 and 11-15 are the subject of this Office Action. This is the first Office Action on the merits of the claims.

Note

The species elected by the applicant is free of the art. The search was extended to a next species.

Priority

2. The current application is a 371 of PCT/EP04/07442 filed on 07/07/2004, which claims priority benefit of provisional application 60/485870 (07/08/2003).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-8, 11-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for L as pyrazole and W as phenyl-oxazol, does not reasonably provide enablement for the remaining scope of rings which include other 5-membered aromatic heterocycles with up to 3 heteroatoms in different positions for L and 3-to7-membered monocyclic or 8-to 12-membered bicyclic rings unsusbstituted or substituted with heteroatoms, tricyclic rings, cycloalkyls of any size and heterocyclic rings which are not oxazole for W. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. There is no

reasonable basis for assuming that the myriad of compounds embraced by the all generic claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims recite a compound of formula (I) with many different variables. These are benzenesulfonamides with N-heterocyclic substituents.

Breadth of the Claims: The claims cover millions of compounds given the number of possible rings, ring systems covered by the claims scope along with varying choices for remaining variables.

State of the prior art: Prior art teaches N-isoxaxole benzenesulfonamides substituted with thio-oxadiazoles or triazoles (*J. Indian Chem. Soc*. **1991**; 68(10):576-578). The claimed compounds are N-pyrazole benzenesulfonylamide compounds substituted with phenyl-oxazol. The latter compounds are not known in the prior art, neither their use nor activity. Nothing in the prior art or current specification disclose sufficient guidance as to how these could be used.

Existence of working examples/specification: The specification does not disclose any compounds besides the N-pyrazole benzenesulfonylamino compounds substituted with

phenyl-oxazol. There is also no test data for any compounds of formula (I) in the specification. Thus, designing any of so many possibilities of the compound of formula (I) as generically claimed and predicting the outcome seems impossible. Currently, a clear evaluation of which rings attached at various ring positions out of the many claimed is needed.

The skill of those in the art: The examiner notes that the knowledge of level of skill in this art would not permit one skilled in this art to assert an intended use for the different variations of compounds of formula (I) claimed and the skilled artisan would not immediately envisage the invention claimed. Additionally, the prior art and disclosure are silent about examples of such compounds other than the mentioned and how to make or how to use them.

Amount of experimentation necessary: The invention is pharmaceutical in nature as it involves treatment of different diseases with the claimed compounds.

In order to practice the claimed invention one of ordinary skill in the art would need to make the very variable claimed compounds by different methods, test them for their activity (including in vivo), investigate their bioavailability, and investigate the effective amount of compound(s) and regimen of administration needed for treating the diseases. It would require undue experimentation for one of ordinary skill in the art to practice the claimed invention in the full broad scope recited in the claims. Therefore, the claimed invention is not fully enabled by the instant specification.

4. Claims 1-8 and 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability or unpredictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims recite a compound of formula (I) with many different variables, clinical use of these compounds and the pharmacokinetic behavior of substances in the human body. These are benzenesulfonamides with N-heterocyclic substituents.

Breadth of the Claims: The instant claims include hundreds of thousands of compounds of formula (I) as recited in claim 1 as well as the presently unknown list of potential prodrug derivatives embraced by claims 1-8 and 11-15.

Guidance of the specification: The direction concerning the prodrugs is found in the instant specification (p8, lines 1-12).

State of the prior art: Wolff (Medicinal Chemistry) summarizes the state of the prodrug art (Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977). The table on the left side on page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since the prodrug concept is a pharmacokinetic issue, the lack of any standard

pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker et al. in the first sentence of third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug (Banker et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596).

Existence of working examples/specification: There is no working example of a prodrug of a compound represented by the formula (I).

The skill of those in the art: Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

The predictability or unpredictability of the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Amount of experimentation necessary: Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed compound, for example, is in fact a prodrug, that produces the active compound metabolically in man at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

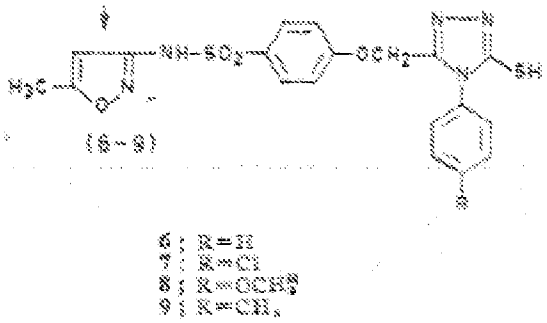
MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Vidyasagar *et al*. (*J. Indian Chem. Soc*. **1991**; 68(10):576-578).

Vidyasagar *et al*. disclose the compound (p. 77):



Where Z= oxygen, p=1, Q= bond, W= 5-membered aromatic heterocycle and L= oxadiazole.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to VALERIE RODRIGUEZ-GARCIA whose telephone number is (571)270-5865. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Joseph McKane can be reached on 571-270-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

VRG

/Kamal A Saeed, Ph.D./

Primary Examiner, Art Unit 1626